

ASSOCIATION OF COMMUNITY
CANCER CENTERS

UNDERSTANDING THE LANDSCAPE
AND INTEGRATION OF
PATHOLOGY WITH THE
COMMUNITY CANCER CARE TEAM



Association of Community Cancer Centers

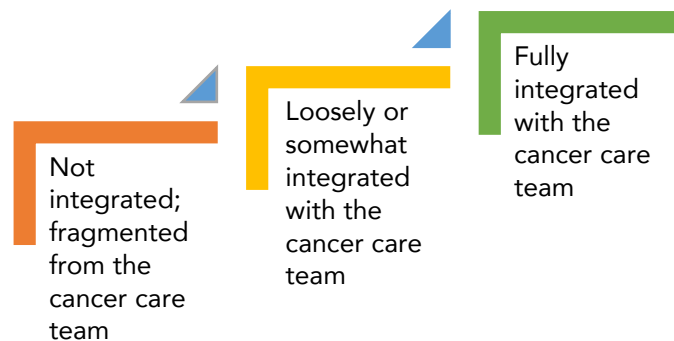
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Introduction

In an era of precision medicine and rapidly advancing cancer therapeutics, the role of pathology in the diagnosis and management of cancer is evolving. Pathologists are uniquely positioned at the intersection of multiple points along the cancer care continuum. Starting at the point of cancer diagnosis, pathologists provide expert interpretation and may recommend biomarker testing to guide treatment decisions. As clinicians monitor treatment response, repeat biopsies or biomarker testing may inform how the tumor is evolving. Pathologists may also play a role in determining clinical trial eligibility, especially for patients who do not respond to the standard of care. Recent advances in targeted therapies, molecular biology, and immuno-oncology necessitate a closer integration and coordination of pathology with the multidisciplinary cancer care team. There are currently no formally established criteria to classify the levels of integration between pathology and the multidisciplinary cancer care team. The Association of Community Cancer Centers (ACCC), joined with partner organizations the Association for Molecular Pathology (AMP), the American Society for Clinical Pathology (ASCP), and the College of American Pathologists (CAP), is working to better understand the current landscape of how pathology is integrated with the cancer care team.

ACCC will broadly assess levels of pathology integration as:

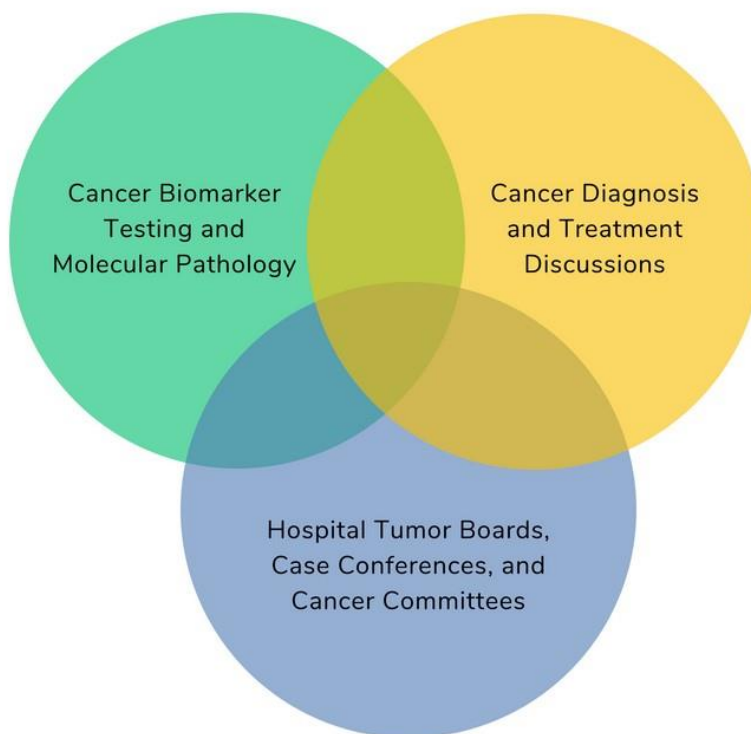


More specifically, ACCC will assess levels of integration in the following key areas:

- Communication and coordination between pathology and the specialists performing biopsies or obtaining tissue samples for the diagnosis of cancer
- Level of involvement by pathology at hospital tumor boards, case conferences, and cancer committee meetings
- Communication and coordination between pathology and the multidisciplinary cancer care team when initial treatment plans are being discussed and developed, when assessing treatment response, when considering additional lines of therapies, and when exploring potential clinical trial participation
- Access to patient records and imaging studies by pathologists and members of the lab team
- Level of involvement by pathology when developing policies or protocols for new cancer diagnostic testing or treatment
- Communication of testing results to the patients

Central Topics

These broad and overlapping topics are deeply interwoven in hospital-based cancer programs where multidisciplinary teams often meet to discuss patient care. Key highlights from a 2018 ACCC survey (May – June 2018, n=659) and recent publications are summarized below to provide an overview of the current landscape of pathology integration with the cancer care team.



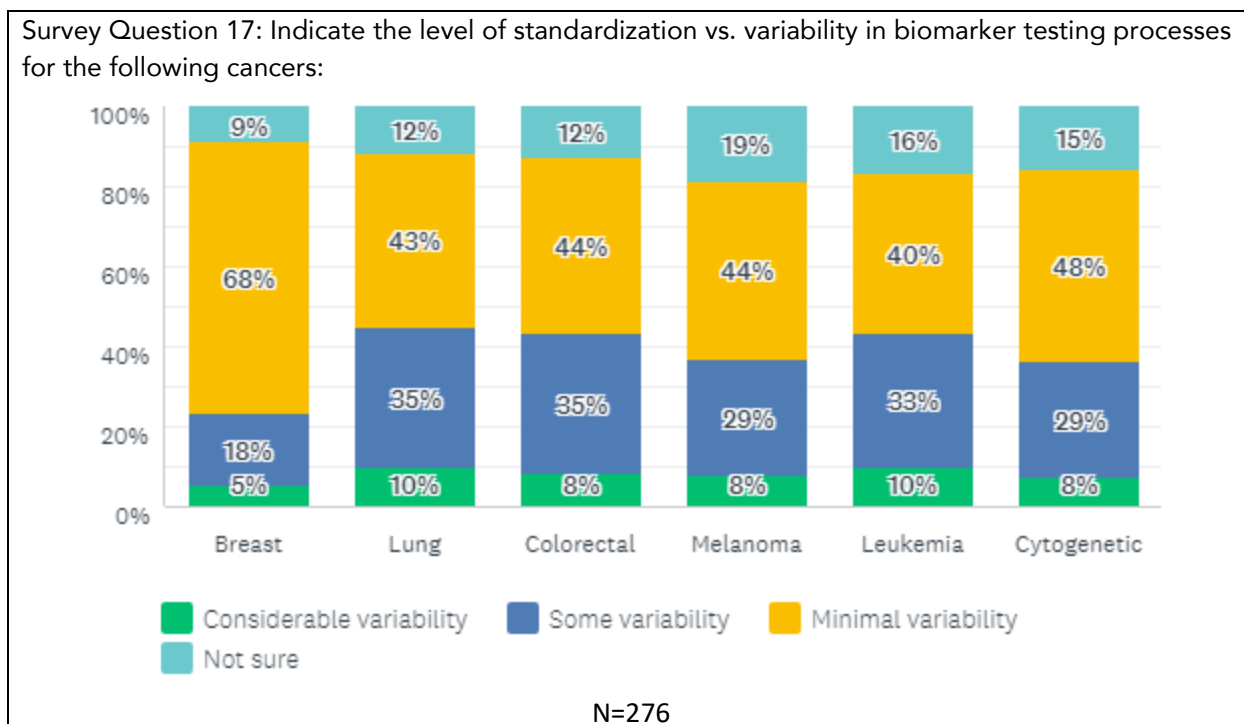
Cancer Biomarker Testing and Molecular Pathology

Biomarker testing processes and policies

As biomarkers become increasingly important to inform treatment decisions, clinicians must decide: *Which biomarker tests should be ordered? Who should order biomarker tests? and Where should the tests be performed?* For certain tumor types, standardized biomarker testing has become routine (e.g., ER/PR/HER2 for breast cancer). For many other tumor types, the evolving landscape of biomarker testing continues to grow more complex as oncologists consider the use of targeted therapy and immunotherapy based on biomarker test results.

- The key considerations for pathologists include tissue availability, ownership of archival tissue, type of diagnostic/biomarker test required, method of sample processing, concordance between different tests and testing centers, and tumor heterogeneity. (Han HS, Magliocco AM. *Clin Breast Cancer*. 2016)
- “The field is rich with opportunities for investigation into biomarkers of immunotherapy response, particularly in the form of collaborative, multidisciplinary studies that incorporate oncologists, pathologists, and basic scientists. Pathologists must take the lead in the rational incorporation of these biomarkers into clinical practice.” (Sholl LM, et al. *Arch Pathol Lab Med*. 2016)

- Results from the ACCC survey reveal that pathologists are often authorized to order some biomarker tests. While 43% of all respondents indicate that their pathologists are authorized to order all types of cancer biomarker tests, 34% report that pathologists may only order certain tests.¹
- ACCC survey reveals a mix of in-house and outside lab biomarker testing. The most common type of tumor biomarker testing that respondents report performing in-house is breast cancer (46%). Across all respondents, 13-25% use a combination of in-house and outside lab testing.²
- Biomarker testing may be more standardized for certain types of cancers. For example, almost every patient with breast cancer will routinely have ER/PR/HER2 testing. In non-small cell lung cancer (NSCLC), tissue samples may be limited and there may be more variability in the types of biomarkers that are ordered. The ACCC survey finds the most standardization for breast cancer biomarker testing and wide variability in testing for lung, colorectal, and leukemia.



Expertise in genomics and molecular pathology

The growing complexity of cancer genomics and genetics is changing the landscape of testing and interpretation. Many smaller cancer programs do not have enough dedicated experts in molecular pathology or cancer genetics on their staff. The science of genomics and genetics is rapidly expanding based on our understanding of how somatic and germline (hereditary) mutations lead to cancer. While most targeted therapies have focused on somatic tumor mutations, we now have drugs that are approved for patients with cancer who have certain germline (hereditary) mutations.

- In the ACCC survey, 56% of all respondents indicated that they have molecular pathologists and 24% indicated that they have a cancer genetics team.³
- “To optimize cancer treatment, we need to understand tumor biology in much more detail on morphological, genetic, proteomic as well as epigenetic grounds.” (Dietel M, et al. *Cancer Gene Ther.* 2015)

- “The lack of a proper model or trained pathologists to support the diagnostic and research missions makes MP [molecular pathology] a rare commodity overall.” (Salto-Tellez M, et al. *Mol Oncol*. 2014)

Medicare coverage for NGS

On March 16, 2018, the Centers for Medicare and Medicaid Services (CMS) announced that it had finalized its [National Coverage Determination \(NCD\) for diagnostic laboratory tests using Next-Generation Sequencing \(NGS\) for patients with advanced cancer](#). “CMS finalized a National Coverage Determination that covers diagnostic laboratory tests using Next Generation Sequencing (NGS) for patients with advanced cancer (i.e., recurrent, metastatic, relapsed, refractory, or stages III or IV cancer).”⁴

- 57% of ACCC survey respondents reported that they were either not aware or unsure about how this change would impact molecular testing.⁵
- During several sessions at the ASCO Annual Meeting 2018, presenters remarked that several unanswered questions remain pertaining to the interpretation of the NCD. Speakers mentioned that it is still unclear whether CMS will cover repeat NGS testing, when a different NGS test is used; whether local coverage determinations (LCDs) will differ from the NCD; and whether testing can be performed to match patients to clinical trials.

Expanding use of NGS and ctDNA

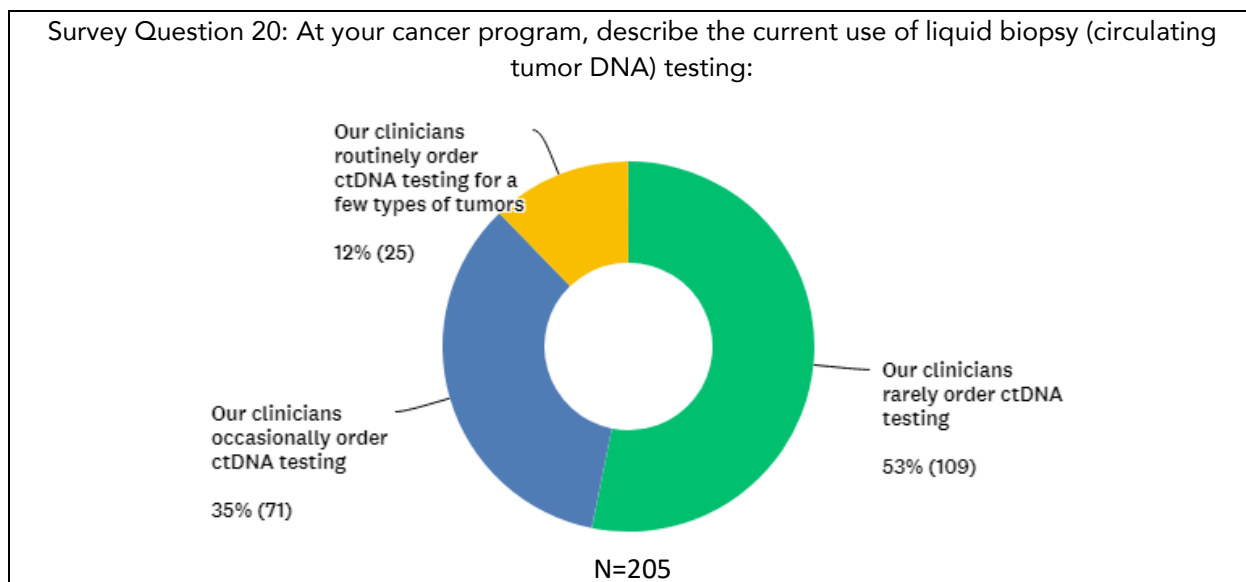
There is considerable variation in the use of Next-Generation Sequencing (NGS) and liquid biopsy (circulating tumor DNA or ctDNA). As of June 2018, the FDA has approved three NGS tumor profiling tests:⁶

- Thermo Fisher Scientific’s OncoPrint Dx Target Test
- MSK-IMPACT
- Foundation Medicine’s FoundationOne CDx

As the use of NGS expands, cancer programs need ongoing guidance on the appropriate use of these testing platforms.

- “Traditional diagnostic pathology has been completely revolutionized by the introduction of next-generation technologies, which provide multigene, targeted mutational profiling, even in the most complex of clinical cases. Combining traditional and molecular knowledge, pathologists integrate the morphological, clinical, and molecular dimensions of a disease, leading to a proper diagnosis and, therefore, the most-appropriate tailored therapy.” (Fassan M. *Arch Pathol Lab Med*. 2018)
- At ASCO 2018, presentations highlighted how the emergence of tumor mutational burden (TMB) as a predictive biomarker for immunotherapy may lead to an increase in the use of NGS. Several presentations also highlighted the recent FDA-approval of NGS tests and the CMS announcement regarding reimbursing for NGS testing in patients with advanced cancer.
- Presentations at ASCO 2018 highlighted the utility of ctDNA when biopsy materials are insufficient, and the patient is unable to undergo a second biopsy; when looking for resistance patterns (e.g., EGFR T790M in NSCLC).
- In the ACCC survey, 53% all respondents reported that their cancer clinicians routinely order NGS testing for “one or two types of tumors” or “several different types of tumors.”⁷

- The survey results were analyzed further by filtering responses based on the number of tumor boards held at respondents' cancer programs. 28% of cancer programs that hold 1 general tumor board routinely use NGS; 42% of those holding 2-3 tumor boards routinely use NGS; and 64% of those holding 4 or more tumor boards routinely use NGS.
- In the ACCC survey, 53% indicated that their clinicians rarely order ctDNA.⁸



Medicare 14-day rule

On November 30, 2017, the Centers for Medicare & Medicaid (CMS) announced revisions to the “Laboratory Date of Service (DOS) Policy,” also known as the 14-Day Rule. These changes went into effect January 1, 2018. CMS “added an exception to the current laboratory DOS regulations, effective January 1, 2018. This new exception to the laboratory DOS policy generally permits laboratories to bill Medicare directly for Advanced Diagnostic Laboratory Tests (ADLTs) and molecular pathology tests excluded from Hospital Outpatient Prospective Payment System (OPPS) packaging policy if the specimen was collected from a hospital outpatient during a hospital outpatient encounter and the test was performed following the patient’s discharge from the hospital outpatient department...”⁹

- In the ACCC survey, 60% reported that they were either not aware or unsure about how this change would impact molecular testing.¹⁰
- An article published on *CAP Today* notes some of the confusion and uncertainty behind this new policy: “labs still aren’t really certain about implementation of regulations, especially by their MACs [Medicare Administrative Contractors]. And they’re reluctant to put processes into place based on interpretations of regulations and potentially have them result in claim denials. They want it clear-cut, so they are really in a ‘wait and see’ mode, and will submit claims and watch for denials.”¹¹

Cancer Diagnosis and Treatment Discussions

Improving cancer diagnosis

In February 2018, the National Cancer Policy Forum held a meeting titled, [Improving Cancer Diagnosis and Care: Patient Access to Oncologic Imaging and Pathology Expertise and Technologies: A Workshop](#). This meeting was designed to examine strategies to ensure that patients have access to appropriate oncologic pathology and imaging expertise and technologies to inform their cancer diagnosis, treatment planning, assessment of treatment response, and oncologic surveillance. Some of the key topics included the following:

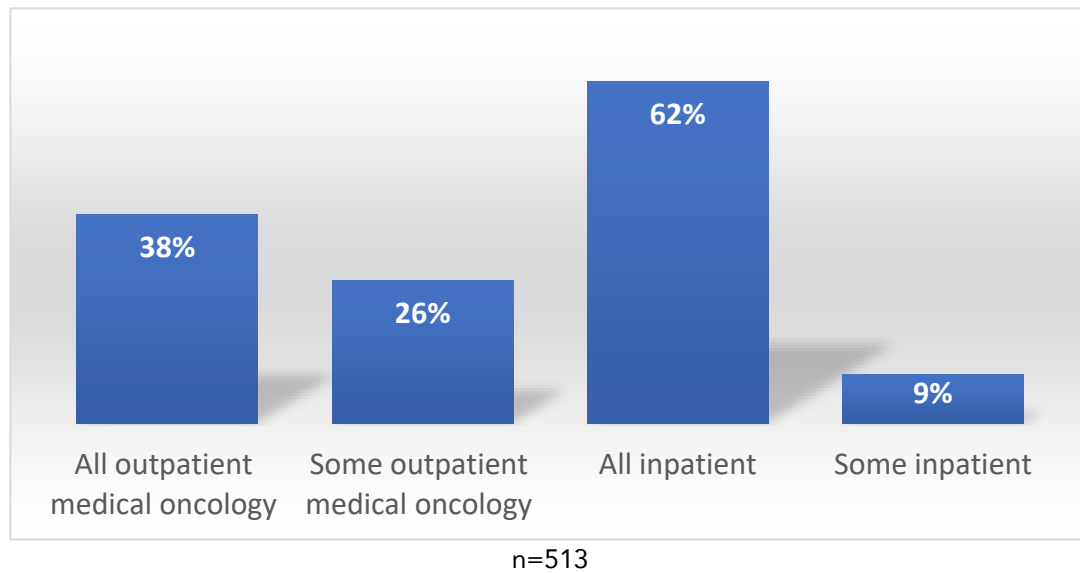
- Training needs for clinicians who interpret pathology and imaging results for patients with cancer.
- Models of care that can improve patient access to cancer specialists in pathology and radiology and implications for patient outcomes and clinical practice.
- Opportunities to enhance collaboration among pathologists, radiologists, and oncologists to improve diagnostic testing and treatment decision-making for patients with cancer.
- Challenges and opportunities for technologies to facilitate improved diagnostic decision-making among specialists and generalists.
- Potential role of new advances in imaging and pathology technologies to improve decision-making for patients with cancer.

Patient records and integrated diagnostic reports

Pathologists ought to have complete access to inpatient and outpatient records. Unfortunately, many pathologists work in settings where they have limited access to patient records. As a result, they may have an incomplete picture of the patient's history and limited access to radiologic reports when making a diagnosis of cancer.

- "The current paradigm of cancer diagnosis involves uncoordinated communication of findings from radiology and pathology to downstream physicians. With the increasing complexity of medicine and the movement toward team-based disease management, there is a need for improved clinical communication and information exchange." (Arnold CW, et al. *Acad Radiol*. 2016)
- The concept of an integrated diagnostic report combines multiple specialties (e.g., pathology, radiology, surgery) and generates an integrated, cross-disciplinary diagnostic approach.¹² These ideas were discussed by radiologists at the 2014 RSNA (Radiological Society of North America) meeting.¹³ In practice, very few organizations have implemented these types of integrated reports.¹⁴
- A recent online editorial highlights the need to improve communication between pathologists and clinicians through regular intradepartmental communication that identifies and shares new diagnostic information and offers practical advice on ways to access pathology services.¹⁵
- In the ACCC survey, 62% indicated that pathologists have access to all inpatient records and 38% indicated they had access to all outpatient medical oncology records.¹⁶

Survey Question 7: Indicate the types of patient health records that your pathologists can directly access: (select all that apply)



Communication between pathologists and cancer clinicians

Advances in understanding of cancer biology has led to more targeted treatment options. The role of pathology in an era of precision medicine continues to evolve and pathologists are becoming more integrated into the clinical cancer care team.

- A recent online editorial highlights the importance of “expanding roles for pathologists as members of the multidisciplinary cancer care team” by emphasizing how pathologists can collaborate closely with oncology colleagues and provide valuable input at diagnosis, biomarker testing, clinical trial considerations, and quality measurement.¹⁷
- In the ACCC survey, 37% of all respondents report that “pathologists occasionally or frequently recommend treatment options during tumor board discussions.”¹⁸
- In another online article, pathologists remarked how “information provided by pathological assessment is far more detailed and clinically-guided than before. The information provided by pathologists is dynamically adapted based on the point of the patient’s management and what is required at a given time in the patient’s journey: the information which must be provided on a biopsy is different from that needed from a surgical specimen, which is in turn different from that needed on a biopsy of recurrent disease.”¹⁹
- “In the future, the role of the pathologist will continue to grow and become fully integrated with clinical care.” (Gazdar AF. *Lung Cancer Management*. 2012)
- “Histological subtyping and molecular testing has become of paramount importance...These have enhanced the clinical relevance of pathological diagnosis, and emphasize the role of the modern surgical pathologist as an integral member of the multidisciplinary team, playing a crucial role in clinical trials and determining appropriate and timely management for patients with lung cancer.” (Davidson MR, et al. *J Thoracic Dis*. 2013)

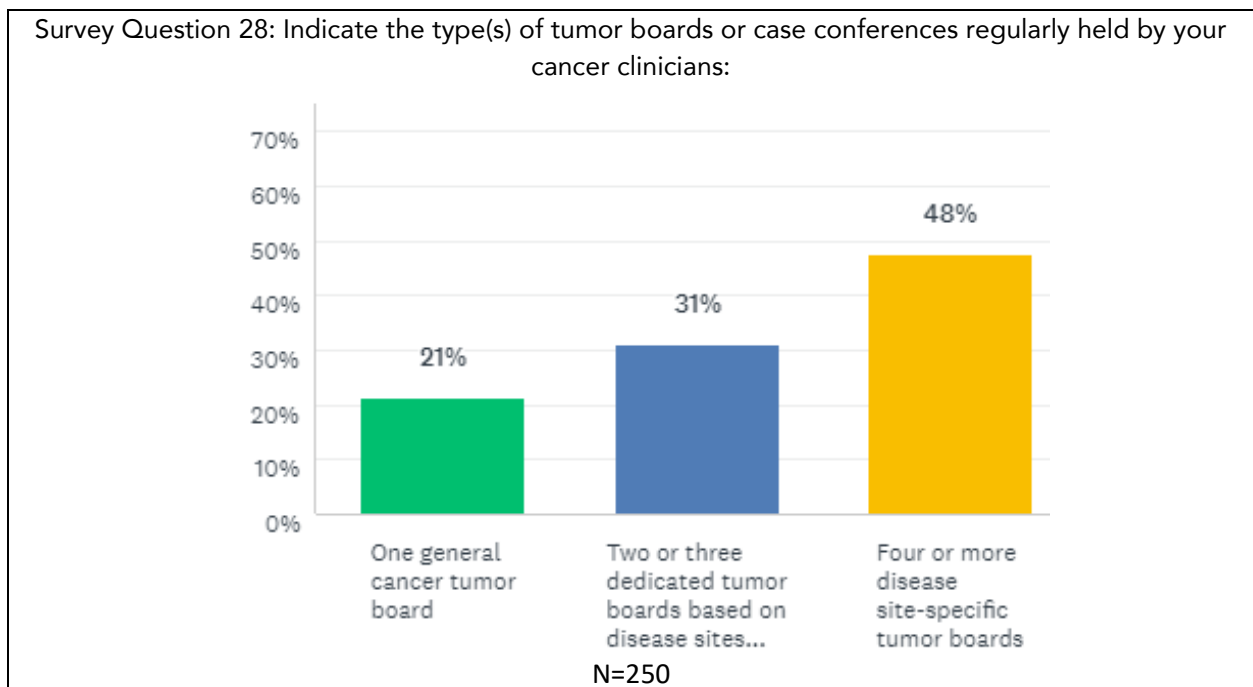
- “The intensified cooperation of clinicians and pathologists will provide the basis of improved clinical drug selection...” (Dietel M. *Oncol Res Treat.* 2016)

Hospital Tumor Boards, Case Conferences, and Cancer Committee

Tumor boards

While many hospital-based cancer programs hold multiple types of tumor boards on a regular basis, smaller hospitals may only hold one general tumor board. Tumor boards may be the only time for multidisciplinary discussion about specific cancer treatment decisions. Attendance by pathology at tumor boards can be variable.

- The ACCC survey asked respondents about their types of tumor boards: 21% indicated that they hold one general tumor board, 31% have two or three dedicated tumor boards, and 48% have four or more disease-specific tumor boards.²⁰



- ACCC survey respondents were also asked about regular tumor board attendance (i.e., more than 75% of tumor board meetings) by their pathologists, and the results indicate that smaller hospitals that hold fewer tumor boards may also have less pathology attendance:²¹

	One general cancer tumor board	Two or three disease-site-specific tumor boards	Four or more disease-site-specific tumor boards
% of respondents who indicate their pathologists “regularly attend over 75%” of the tumor board meetings	66%	73%	83%

Discussing treatment plans

Tumor boards have been shown to change treatment decisions when a group of multidisciplinary clinicians discuss optimal management strategies. At some cancer programs, every patient with cancer is discussed at a tumor board. At other cancer programs, only select patients are presented and discussed.

- “Routine discussion of all urologic oncology cases at MTB (multidisciplinary tumor board) led to a change in treatment plan in 17.8% of patients.” (Scarberry K, et al. *Can Urol Assoc J.* 2018)
- “Gynecologic oncology MTBCs resulted in considerable changes in treatment plans.” (Lee B, et al. *Medicine* (Baltimore). 2017)
- “Multidisciplinary team (MDT) meetings for patients with a GI malignancy are responsible for changes in diagnoses and management in a significant number of patients.” (Basta YL, et al. *Ann Surg Oncol.* 2017)
- “Patients discussed at MDT meetings were more likely to receive more accurate and complete pre-operative staging, and neo-adjuvant/adjuvant treatment.” (Pillay B, et al. *Cancer Treat Rev.* 2016)
- “The MTB recommendations changed treatment plans in 40% and staging and assessment plans in 60% of patients.” (Schmidt HM, et al. *Ann Thorac Surg.* 2015)

Clinical Practice Guideline Collaborations

The following table shows recent collaborations between the American Society of Clinical Oncology (ASCO) and pathology organizations [Association for Molecular Pathology (CAP), American Society for Clinical Pathology (ASCP), and College of American Pathologists (CAP)] related to the development and/or endorsement of clinical practice guidelines:

	Date	ASCO	AMP	ASCP	CAP
Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer Update	November 1, 2013; Updated May 30, 2018	X			x
Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer	July 20, 2015	X			
HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma	November 14, 2016	X		x	x
Molecular Biomarkers for the Evaluation of Colorectal Cancer	February 6, 2017	X	x	x	x
Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer	July 10, 2017	X			
Molecular Testing for the Selection of Patients with Lung Cancer for Treatment with Targeted Tyrosine Kinase Inhibitors Guideline Endorsement (IASLC)	February 5, 2018	(IASLC) ASCO endorsement	x		x
Circulating Tumor DNA Analysis in Patients With Cancer: An ASCO/CAP Joint Review	March 5, 2018	x			x

Evolving Themes and Future Direction

Technology

Recent advances in pathology informatics include digital pathology, whole slide imaging, and the use of machine learning and artificial intelligence. While many of these changes are being driven in academic institutions, some of these tools and platforms are reaching community practices. In April 2017, the FDA approved the first whole slide imaging system for digital pathology.²² The use of digital pathology is expected to make it easier to share cases, balance workload, centralize services, and support subspecialty practice.²³

An article published in December 2017 showed how researchers had demonstrated that deep learning algorithms performed significantly better than a panel of 11 pathologists in a diagnostic simulation for detecting lymph node metastases.²⁴ A number of academic centers like the Ohio State University have launched digital pathology platforms, but it may still take a year or longer for them to be fully integrated into clinical care.²⁵

In October 2018, the National Cancer Policy Forum will hold a workshop on, "Improving Cancer Diagnosis and Care: The Clinical Application of Computational Methods in Precision Oncology: A Workshop."²⁶ The workshop will feature invited presentations and panel discussions on topics that may include:

- Challenges and opportunities to use omics data to develop precision medicine approaches and technologies in cancer care
- Potential standards and best practices for computational software and methodological approaches for the use of big data to inform the care of patients with cancer, especially regarding multi-parameter/multi-treatment testing and interpretation
- Potential opportunities to improve the translation of omics technologies into oncology practice

Summary

Advances in cancer research are necessitating greater integration between pathology and the cancer care team. The expansion of biomarker testing, molecular pathology and targeted therapies has led to more collaboration between pathology and clinical oncology. Ongoing research in the areas of germline (hereditary) mutations and immunotherapy is continuing to drive the need to have pathology and oncology more closely integrated than in the past. While prognostic and predictive biomarkers continue to grow in clinical use, oncologists and pathologists also need to have a deeper understanding behind the basic science of tumor biology and the microenvironment. There are numerous ways that pathology can become more deeply and tightly integrated with the cancer care team so that patients are receiving appropriate and timely care in the community.

Publication Abstracts

Arnold CW, Wallace WD, Chen S, Oh A, Abtin F, Genshaft S, Binder S, Aberle D, Enzmann D. RadPath: A Web-based System for Integrating and Correlating Radiology and Pathology Findings During Cancer Diagnosis. *Acad Radiol.* 2016 Jan;23(1):90-100.

RATIONALE AND OBJECTIVES: *The current paradigm of cancer diagnosis involves uncoordinated communication of findings from radiology and pathology to downstream physicians.* Discordance between these

findings can require additional time from downstream users to resolve, or given incorrect resolution, may adversely impact treatment decisions. To mitigate this problem, we developed a web-based system, called RadPath, for correlating and integrating radiology and pathology reporting.

MATERIALS AND METHODS: RadPath includes interfaces to our institution's clinical information systems, which are used to retrieve reports, images, and test results that are structured into an interactive compendium for a diagnostic patient case. The system includes an editing interface for physicians, allowing for the inclusion of additional clinical data, as well as the ability to retrospectively correlate and contextualize imaging findings following pathology diagnosis.

RESULTS: During pilot deployment and testing over the course of 1 year, physicians at our institution have completed 60 RadPath cases, requiring an average of 128 seconds from a radiologist and an average of 93 seconds from a pathologist per case. Several technical and workflow challenges were encountered during development, including interfacing with diverse clinical information systems, automatically structuring report contents, and determining the appropriate physicians to create RadPath summaries. Reaction to RadPath has been positive, with users valuing the system's ability to consolidate diagnostic information.

CONCLUSIONS: *With the increasing complexity of medicine and the movement toward team-based disease management, there is a need for improved clinical communication and information exchange.* RadPath provides a platform for generating coherent and correlated diagnostic summaries in cancer diagnosis with minimal additional effort from physicians.

Basta YL, Bolle S, Fockens P, Tytgat KMAJ. The Value of Multidisciplinary Team Meetings for Patients with Gastrointestinal Malignancies: A Systematic Review. Ann Surg Oncol. 2017 Sep;24(9):2669-2678.

INTRODUCTION: The incidence of gastrointestinal (GI) cancer is rising and most patients with GI malignancies are discussed by a multidisciplinary team (MDT). We performed a systematic review to assess whether MDTs for patients with GI malignancies can correctly change diagnosis, tumor stage and subsequent treatment plan, and whether the treatment plan was implemented.

METHODS: We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We conducted a search of the PubMed, MEDLINE and EMBASE electronic databases, and included studies relating to adults with a GI malignancy discussed by an MDT prior to the start of treatment which described a change of initial diagnosis, stage or treatment plan. Two researchers independently evaluated all retrieved titles and abstracts from the abovementioned databases.

RESULTS: Overall, 16 studies were included; the study quality was rated as fair. Four studies reported that MDTs changed the diagnoses formulated by individual physicians in 18.4-26.9% of evaluated cases; two studies reported that MDTs formulated an accurate diagnosis in 89 and 93.5% of evaluated cases, respectively; nine studies described that the treatment plan was altered in 23.0-41.7% of evaluated cases; and four studies found that MDT decisions were implemented in 90-100% of evaluated cases. The reasons for altering a treatment plan included the patient's wishes, and comorbidities.

CONCLUSIONS: *MDT meetings for patients with a GI malignancy are responsible for changes in diagnoses and management in a significant number of patients.* Treatment plans formulated by MDTs are implemented in 90-100% of discussed patients. All patients with a GI malignancy should be discussed by an MDT.

Budczies J, Bockmayr M, Denkert C, Klauschen F, Lennerz JK, Györfy B, Dietel M, Loibl S, Weichert W, Stenzinger A. Classical pathology and mutational load of breast cancer - integration of two worlds. *J Pathol Clin Res.* 2015 Jul 20;1(4):225-38.

Breast cancer is a complex molecular disease comprising several biological subtypes. However, daily routine diagnosis is still based on a small set of well-characterized clinico-pathological variables. Here, we try to link the two worlds of surgical pathology and multilayered molecular profiling by analyzing the relationships between clinico-pathological phenotypes and mutational loads of breast cancer. We evaluated the number of mutated genes with somatic non-silent mutations in different subgroups of breast cancer based on clinico-pathological, including immunohistochemical and tumour characteristics. The analysis was performed for a cohort of 687 primary breast cancer patients with mutational profiling, gene expression and clinico-pathological data available from The Cancer Genome Atlas (TCGA) project. The number of mutated genes was strongly positively associated with higher tumour grade ($p = 1.4e-14$) and with the different immunohistochemical and PAM50 molecular subtypes of breast cancer ($p = 1.4e-10$ and $p = 4.3e-10$, respectively). We observed significant associations ($|R| > 0.4$) between the abundance of mutated genes and expression levels of genes related to proliferation in the overall cohort and hormone receptor positive cohort, including the Recurrence Score gene signature (e.g., MYBL2 and BIRC5). Specific mutated genes (TP53, NCOR1, NF1, PTPRD and RB1) were highly significantly associated with high loads of mutated genes. Multivariate analysis for overall survival (OS) revealed a worse survival for patients with high numbers of mutated genes (hazard ratio = 4.6, 95% CI: 1.0 - 20.0, $p = 0.044$). Here, we report a strong association of the number of mutated genes with immunohistochemical and PAM50 subtypes and tumour grade in breast cancer. We provide evidence that specific levels of the mutational load underlie different morphological and biological phenotypes, which collectively constitute the current basis of pathological diagnosis. *Our study is a step towards genomics-informed breast pathology and will provide a basis for future studies in this field, bridging the gap between morphology, tumour biology, and medical oncology.*

Davidson MR, Gazdar AF, Clarke BE. The pivotal role of pathology in the management of lung cancer. *J Thorac Dis.* 2013;5(Suppl 5):S463-S478. doi:10.3978/j.issn.2072-1439.2013.08.43.

The last decade has seen significant advances in our understanding of lung cancer biology and management. Identification of key driver events in lung carcinogenesis has contributed to the development of targeted lung cancer therapies, heralding the era of personalized medicine for lung cancer. As a result, *histological subtyping and molecular testing has become of paramount importance*, placing increasing demands on often small diagnostic specimens. This has triggered the review and development of the first structured classification of lung cancer in small biopsy/cytology specimens and a new classification of lung adenocarcinoma from the IASLC/ATS/ERS. *These have enhanced the clinical relevance of pathological diagnosis, and emphasize the role of the modern surgical pathologist as an integral member of the multidisciplinary team, playing a crucial role in clinical trials and determining appropriate and timely management for patients with lung cancer.*

Dei Tos AP, Bonvalot S, Haas R. The key role of pathology, surgery and radiotherapy in the initial management of soft tissue sarcoma. *Future Oncol.* 2018 May;14(10s):15-23.

Soft tissue sarcomas are a heterogeneous group of rare malignancies. The diagnostic gold standard is conventional histomorphology with integrated immunohistochemistry. Molecular genetic profiling has identified new subgroups of undifferentiated sarcomas involving genetic rearrangements with creation of fusion genes.

Accurate classification of sarcomas is critical for appropriate clinical decision-making which should involve a multidisciplinary team. A preoperative biopsy is necessary to confirm a diagnosis. Strategy is discussed in the multidisciplinary board. Reconstructive surgery must be planned in advance taking into account possible surgical morbidity. In high-risk situations, neo-adjuvant treatment could facilitate surgery in some cases, increase survival and provide indications of tumor biology. The decision is based on tumor subtype, grade and location, patient age and presence of comorbidities.

De Abreu FB, Wells WA, Tsongalis GJ. The emerging role of the molecular diagnostics laboratory in breast cancer personalized medicine. Am J Pathol. 2013 Oct;183(4):1075-1083.

Breast cancer is a complex disease characterized by many morphological, clinical, and molecular features. For many years, breast cancer has been classified according to traditional parameters, such as histological type, grade, tumor size, lymph node involvement and vascular invasion, and biomarkers (eg, estrogen receptor, progesterone receptor, and epidermal growth factor receptor 2), which are used in patient management. With emerging imaging techniques (ie, digital mammography, tomosynthesis, ultrasonography, magnetic resonance imaging, nuclear medicine, and genomic techniques, such as real-time RT-PCR and microarrays), breast cancer diagnostics is going through a significant evolution. Imaging technologies have improved breast cancer diagnosis, survival, and treatment by early detection of primary or metastatic lesions, differentiating benign from malignant lesions and promoting intraoperative surgical guidance and postoperative specimen evaluation. Genomic and transcriptomic technologies make the analysis of gene expression signatures and mutation status possible so that tumors may be classified more accurately with respect to diagnosis and prognosis. The -omic era has also made possible the identification of new biomarkers involved in breast cancer development, survival, and invasion that can be gradually incorporated into clinical testing. These advances in both imaging and genomics contribute to more personalized and predictive patient management. We review the progress made in breast cancer diagnosis and management using these new tools.

Dietel M. Molecular Pathology: A Requirement for Precision Medicine in Cancer. Oncol Res Treat. 2016;39(12):804-810. Epub 2016 Nov 25.

The increasing importance of targeting drugs in the treatment of several tumor entities (breast, colon, lung, malignant melanoma (MM), lymphoma, and so on) and the necessity of a companion diagnostic (human epidermal growth factor receptor 2, Kirsten rat sarcoma viral oncogene, epidermal growth factor receptor (EGFR), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), and so on) is leading to new challenges for surgical pathology. As all the biomarkers to be specifically detected are tissue based, a precise and reliable diagnostic is absolutely crucial. To meet this challenge, surgical pathology has adapted a number of molecular methods (semi-quantitative immunohistochemistry, fluorescence in situ hybridization), PCR and its multiple variants, (pyro/Sanger) sequencing, next-generation sequencing, DNA-arrays, methylation analyses, and so on) to be applicable for formalin-fixed paraffin-embedded (FFPE) tissue. To read a patients' tissue as 'deeply' as possible and to obtain information on morphological, genetic, proteomic as well as epigenetic background is the actual task of pathologists and molecular biologists in order to provide the clinicians with information relevant for individualized medicine. The intensified cooperation of clinicians and pathologists will provide the basis of improved clinical drug selection as well as guide development of new cancer gene therapies and molecularly targeted drugs by research units and the pharmaceutical industry. This review will give some information on (1) biomarker detection methods adapted to FFPE tissue, (2) the potency of predictive pathology in tumor detection

and treatment and (3) the implications of pathology on the development of new drugs in molecularly targeted and gene therapies.

Dietel M, Jöhrens K, Laffert MV, Hummel M, Bläker H, Pfitzner BM, Lehmann A, Denkert C, Darb-Esfahani S, Lenze D, Heppner FL, Koch A, Sers C, Klauschen F, Anagnostopoulos I. A 2015 update on predictive molecular pathology and its role in targeted cancer therapy: a review focusing on clinical relevance. *Cancer Gene Ther.* 2015 Sep;22(9):417-30.

In April 2013 our group published a review on predictive molecular pathology in this journal. Although only 2 years have passed many new facts and stimulating developments have happened in diagnostic molecular pathology rendering it worthwhile to present an up-date on this topic. A major technical improvement is certainly given by the introduction of next-generation sequencing (NGS; amplicon, whole exome, whole genome) and its application to formalin-fixed paraffin-embedded (FFPE) tissue in routine diagnostics. Based on this 'revolution' the analyses of numerous genetic alterations in parallel has become a routine approach opening the chance to characterize patients' malignant tumors much more deeply without increasing turn-around time and costs. In the near future this will open new strategies to apply 'off-label' targeted therapies, e.g. for rare tumors, otherwise resistant tumors etc. The clinically relevant genetic aberrations described in this review include mutation analyses of RAS (KRAS and NRAS), BRAF and PI3K in colorectal cancer, KIT or PDGFR alpha as well as BRAF, NRAS and KIT in malignant melanoma. Moreover, we present several recent advances in the molecular characterization of malignant lymphoma. Beside the well-known mutations in NSCLC (EGFR, ALK) a number of chromosomal aberrations (KRAS, ROS1, MET) have become relevant. Only very recently has the clinical need for analysis of BRCA1/2 come up and proven as a true challenge for routine diagnostics because of the genes' special structure and hot-spot-free mutational distribution. The genetic alterations are discussed in connection with their increasingly important role in companion diagnostics to apply targeted drugs as efficient as possible. As another aspect of the increasing number of druggable mutations, we discuss the challenges personalized therapies pose for the design of clinical studies to prove optimal efficacy particularly with respect to combination therapies of multiple targeted drugs and conventional chemotherapy. Such combinations would lead to an extremely high complexity that would hardly be manageable by applying conventional study designs for approval, e.g. by the FDA or EMA. Up-coming challenges such as the application of methylation assays and proteomic analyses on FFPE tissue will also be discussed briefly to open the door towards the ultimate goal of reading a patients' tissue as 'deeply' as possible. Although it is yet to be shown, which levels of biological information are most informative for predictive pathology, an integrated molecular characterization of tumors will likely offer the most comprehensive view for individualized therapy approaches. **To optimize cancer treatment, we need to understand tumor biology in much more detail on morphological, genetic, proteomic as well as epigenetic grounds.** Finally, the complex challenges on the level of drug design, molecular diagnostics, and clinical trials make necessary a close collaboration among academic institutions, regulatory authorities and pharmaceutical companies.

Fassan M. Molecular Diagnostics in Pathology: Time for a Next-Generation Pathologist? *Arch Pathol Lab Med.* 2018 Mar;142(3):313-320.

CONTEXT: - Comprehensive molecular investigations of mainstream carcinogenic processes have led to the use of effective molecular targeted agents in most cases of solid tumors in clinical settings.

OBJECTIVE: - To update readers regarding the evolving role of the pathologist in the therapeutic decision-making process and the introduction of next-generation technologies into pathology practice.

DATA SOURCES: - Current literature on the topic, primarily sourced from the PubMed (National Center for Biotechnology Information, Bethesda, Maryland) database, were reviewed.

CONCLUSIONS: - Adequate evaluation of cytologic-based and tissue-based predictive diagnostic biomarkers largely depends on both proper pathologic characterization and customized processing of biospecimens. Moreover, increased requests for molecular testing have paralleled the recent, sharp decrease in tumor material to be analyzed-material that currently comprises cytology specimens or, at minimum, small biopsies in most cases of metastatic/advanced disease. Traditional diagnostic pathology has been completely revolutionized by the introduction of next-generation technologies, which provide multigene, targeted mutational profiling, even in the most complex of clinical cases. Combining traditional and molecular knowledge, pathologists integrate the morphological, clinical, and molecular dimensions of a disease, leading to a proper diagnosis and, therefore, the most-appropriate tailored therapy.

Fennell ML, Das IP, Clauser S, Petrelli N, Salner A. The organization of multidisciplinary care teams: modeling internal and external influences on cancer care quality. J Natl Cancer Inst Monogr. 2010;2010(40):72-80.

Quality cancer treatment depends upon careful coordination between multiple treatments and treatment providers, the exchange of technical information, and regular communication between all providers and physician disciplines involved in treatment. This article will examine a particular type of organizational structure purported to regularize and streamline the communication between multiple specialists and support services involved in cancer treatment: the multidisciplinary treatment care (MDC) team. We present a targeted review of what is known about various types of MDC team structures and their impact on the quality of treatment care, and we outline a conceptual model of the connections between team context, structure, process, and performance and their subsequent effects on cancer treatment care processes and patient outcomes. Finally, we will discuss future research directions to understand how MDC teams improve patient outcomes and how characteristics of team structure, culture, leadership, and context (organizational setting and local environment) contribute to optimal multidisciplinary cancer care.

Gazdar AF. The evolving role of the pathologist in the management of lung cancer. Lung Cancer Manage. 2012;1(4):273-281.

Major advances in pathology, molecular biology, patient diagnosis and care, as well as the advent of personalized therapy, have resulted in a greatly increased role for the pathologist, who has emerged as a key member of the lung cancer management team. A new multidisciplinary, clinically relevant classification of pulmonary adenocarcinoma has resulted in a paradigm shift in how we view and practice lung cancer pathology. In the future, the role of the pathologist will continue to grow and become fully integrated with clinical care.

Gröschel S, Bommer M, Hutter B, Budczies J, Bonekamp D, Heining C, Horak P, Fröhlich M, Uhrig S, Hübschmann D, Georg C, Richter D, Pfarr N, Pfütze K, Wolf S, Schirmacher P, Jäger D, von Kalle C, Brors B, Glimm H, Weichert W, Stenzinger A, Fröhling S. Integration of genomics and histology revises diagnosis and enables effective therapy of refractory cancer of unknown primary with PDL1 amplification. Cold Spring Harb Mol Case Stud. 2016 Nov;2(6):a001180.

Identification of the tissue of origin in cancer of unknown primary (CUP) poses a diagnostic challenge and is critical for directing site-specific therapy. Currently, clinical decision-making in patients with CUP primarily relies on histopathology and clinical features. Comprehensive molecular profiling has the potential to contribute to diagnostic categorization and, most importantly, guide CUP therapy through identification of actionable lesions. We here report the case of an advanced-stage malignancy initially mimicking poorly differentiated soft-tissue sarcoma that did not respond to multiagent chemotherapy. Molecular profiling within a clinical whole-exome and transcriptome sequencing program revealed a heterozygous, highly amplified KRAS G12S mutation, compound-heterozygous TP53 mutation/deletion, high mutational load, and focal high-level amplification of Chromosomes 9p (including PDL1 [CD274] and JAK2) and 10p (including GATA3). Integrated analysis of molecular data and histopathology provided a rationale for immune checkpoint inhibitor (ICI) therapy with pembrolizumab, which resulted in rapid clinical improvement and a lasting partial remission. Histopathological analyses ruled out sarcoma and established the diagnosis of a poorly differentiated adenocarcinoma. Although neither histopathology nor molecular data were able to pinpoint the tissue of origin, our analyses established several differential diagnoses including triple-negative breast cancer (TNBC). We analyzed 157 TNBC samples from The Cancer Genome Atlas, revealing PDL1 copy number gains coinciding with excessive PDL1 mRNA expression in 24% of cases. Collectively, these results illustrate the impact of multidimensional tumor profiling in cases with nondescript histology and immunophenotype, show the predictive potential of PDL1 amplification for immune checkpoint inhibitors (ICIs), and suggest a targeted therapeutic strategy in Chromosome 9p24.1/PDL1-amplified cancers.

Han HS, Magliocco AM. Molecular Testing and the Pathologist's Role in Clinical Trials of Breast Cancer. Clin Breast Cancer. 2016 Jun;16(3):166-79.

Molecular characterization of breast cancer is pivotal for identifying new molecular targets and determining the appropriate treatment choices. Advances in molecular profiling technology have given greater insight into this heterogeneous disease, over and above hormone receptor and human epidermal growth factor receptor 2 status. Agents targeting recently characterized molecular biomarkers are under clinical development; the success of these targeted agents is likely to depend on identifying the patient population most likely to benefit. Therefore, clinical trials of breast cancer often require prescreening for, or stratification by, relevant molecular markers or exploratory analyses of biomarkers that can predict or monitor the response to treatment. Consequently, the role of the pathologist has become increasingly important. The key considerations for pathologists include tissue availability, ownership of archival tissue, type of diagnostic/biomarker test required, method of sample processing, concordance between different tests and testing centers, and tumor heterogeneity. In the present review, we explore how pathology is used in current clinical trials of breast cancer and describe the various technologies available for molecular testing. Furthermore, the factors required for the successful application of pathology in clinical trials of breast cancer and the issues that can arise and how these can be circumvented are discussed.

Hofstraat H, et al. Integrated, structured reporting and diagnosis of localized prostate cancer. J Clin Oncol. 35, no. 15_suppl

Background: To date 80-90% of men with primary prostate cancer are diagnosed with localized disease with a wide range of risks of future tumor progression. To optimize the balance between tumor removal and preserved continence and erectile function, it is essential to integrate all available information on tumor location, tumor characteristics, and baseline clinical data. Methods: We have developed a cloud-web-based technology allowing

flexible access to the clinical data with close integration to the existing IT-environment like the hospital information management systems. **The system allows the systematic and structured reporting of medical data generated by the involved disciplines of urology, laboratory, radiology, pathology, and (radiation) oncology, and patient reported health status and outcomes.** Results: By use of the developed data integration platform we have collected diagnostic data of a prostate cancer case example scheduled for a multi-disciplinary primary treatment decision. The data comprises the patient health conditions, laboratory measures, multi-parametric MRI, localization information of MRI/US fusion guided biopsies, histo-pathology outcomes of prostate biopsy specimen, and patient reported outcomes on urinary and sexual function status. The collected data was presented in a visually integrated way and was used to discuss in a multi-disciplinary team, with the consistencies or discordances of findings across the various medical domains involved. Based on the discussion a primary treatment decision was concluded for this patient. Conclusions: The developed IT system to integrate heterogeneous medical data was successfully tested in a multi-disciplinary clinical setting. All required clinical variables to provide an informed primary treatment decision for a patient with primary localized prostate cancer was available in the system for discussion during the multi-disciplinary team (MDT) meeting and was presented in a clear visual way to support the interactive discussions between MDT members representing different clinical specialties.

Horak P, Fröhling S, Glimm H. Integrating next-generation sequencing into clinical oncology: strategies, promises and pitfalls. ESMO Open. 2016;1(5):e000094.

We live in an era of genomic medicine. The past five years brought about many significant achievements in the field of cancer genetics, driven by rapidly evolving technologies and plummeting costs of next-generation sequencing (NGS). The official completion of the Cancer Genome Project in 2014 led many to envision the clinical implementation of cancer genomic data as the next logical step in cancer therapy. Stemming from this vision, the term 'precision oncology' was coined to illustrate the novelty of this individualised approach. The basic assumption of precision oncology is that molecular markers detected by NGS will predict response to targeted therapies independently from tumour histology. However, along with a ubiquitous availability of NGS, the complexity and heterogeneity at the individual patient level had to be acknowledged. Not only does the latter present challenges to clinical decision-making based on sequencing data, it is also an obstacle to the rational design of clinical trials. Novel tissue-agnostic trial designs were quickly developed to overcome these challenges. Results from some of these trials have recently demonstrated the feasibility and efficacy of this approach. On the other hand, there is an increasing amount of whole-exome and whole-genome NGS data which allows us to assess ever smaller differences between individual patients with cancer. In this review, we highlight different tumour sequencing strategies currently used for precision oncology, describe their individual strengths and weaknesses, and emphasise their feasibility in different clinical settings. Further, we evaluate the possibility of NGS implementation in current and future clinical trials, and point to the significance of NGS for translational research.

Lamb BW, Green JS, Benn J, Brown KF, Vincent CA, Sevdalis N. Improving decision making in multidisciplinary tumor boards: prospective longitudinal evaluation of a multicomponent intervention for 1,421 patients. J Am Coll Surg. 2013 Sep;217(3):412-20.

BACKGROUND: Due to its complexity, cancer care is increasingly being delivered by multidisciplinary tumor boards (MTBs). Few studies have investigated how best to organize and run MTBs to optimize clinical decision

making. We developed and evaluated a multicomponent intervention designed to improve the MTB's ability to reach treatment decisions.

STUDY DESIGN: We conducted a prospective longitudinal study during 16 months that evaluated MTB decision making for urological cancer patients at a university hospital in London, UK. After a baseline period, MTB improvement interventions (eg, MTBs checklist, MTB team training, and written guidance) were delivered sequentially. Outcomes measures were the MTB's ability to reach a decision, the quality of information presentation, and the quality of teamwork (as assessed by trained assessors using a previously validated observational assessment tool). The efficacy of the intervention was evaluated using multivariate analyses.

RESULTS: There were 1,421 patients studied between December 2009 and April 2, 2011. **All outcomes improved considerably between baseline and intervention implementation: the MTB's ability to reach a decision rose from 82.2% to 92.7%, quality of information presentation rose from 29.6% to 38.3%, and quality of teamwork rose from 37.8% to 43.0%.** The MTB's ability to reach a treatment decision was related to the quality of available information ($r = 0.298$; $p < 0.05$) and quality of teamwork within the MTB ($r = 0.348$; $p < 0.05$). The most common barriers to reaching clinical decisions were inadequate radiologic information ($n = 77$), inadequate pathologic information ($n = 51$), and inappropriate patient referrals ($n = 21$).

CONCLUSIONS: Multidisciplinary tumor board-delivered treatment is becoming the standard for cancer care worldwide. Our intervention is efficacious and applicable to MTBs and can improve decision making and expedite cancer care.

Lee B, Kim K, Choi JY, Suh DH, No JH, Lee HY, Eom KY, Kim H, Hwang SI, Lee HJ, Kim YB. Efficacy of the multidisciplinary tumor board conference in gynecologic oncology: A prospective study. Medicine (Baltimore). 2017 Dec;96(48):e8089.

Evidence has shown that multidisciplinary tumor board conferences (MTBCs) improve patient management for various cancer types. However, few retrospective studies have investigated MTBC efficacy for patients with gynecologic cancers. Here, we prospectively aimed to evaluate how MTBCs influence patient management in gynecologic oncology. This prospective study included 85 consecutive cases that were presented at gynecologic oncology MTBCs in our tertiary university hospital between January 2015 and April 2016. The primary endpoint was treatment plan change rate, which included both major and minor changes. Major changes were defined as exchange, addition, or subtraction of treatment modality. Minor changes included all other, such as intramodality changes or treatment time changes. The secondary endpoints were the change rates of diagnosis, diagnostic work-up, and radiological and pathological findings. The treatment plan change rate, irrespective of changes in diagnostic work-up, was 27.1%, which included 10.6% major and 16.5% minor changes. Among the treatment plan changes, changes in the treatment plan change rate alone were noted in 16.5% of cases, and changes in diagnosis and radiological findings occurred in 7.1% and 3.5% of cases, respectively. Diagnosis and radiological findings, irrespective of changes in diagnostic work-up, were also changed in 9.4% and 10.6% of cases, respectively. However, there were no changes in pathological findings. Moreover, there was a change of diagnostic method for further work-up in 23.5% of cases. The implementation rate of MTBC-determined treatment changes was 91.8%. **Gynecologic oncology MTBCs resulted in considerable changes in treatment plans.** Diagnosis, diagnostic work-up, and radiological findings were influenced by MTBCs. The data emphasize the importance of adopting a multidisciplinary team approach for gynecologic cancer management.

Lee SJ, Clark MA, Cox JV, Needles BM, Seigel C, Balasubramanian BA. Achieving Coordinated Care for Patients With Complex Cases of Cancer: A Multiteam System Approach. *J Oncol Pract.* 2016 Nov;12(11):1029-1038. Epub 2016 Oct 31.

Patients with cancer with multiple chronic conditions pose a unique challenge to how primary care and specialty care teams provide well-coordinated, patient-centered care. Effectiveness of these care teams in providing optimal health care depends on the extent to which they coordinate their goals and knowledge as components of a multiteam system (MTS). This article outlines challenges of care coordination in the context of an MTS, illustrated through the care experience of "Mr Fuentes," a patient in the Dallas County integrated safety-net system, Parkland. As a continuing patient with chronic illnesses, the patient being discussed is managed through one of the Parkland community-oriented primary care clinics. However, a cancer diagnosis triggered an additional need for augmented coordination between his different provider teams. Further research and practice should investigate the relationships of MTS coordination for shared care management, transfer to and from specialty care, treatment compliance, barriers to care, and health outcomes of chronic comorbid conditions, as well as cancer control and surveillance.

Nagtegaal ID, West NP, van Krieken JH, Quirke P. Pathology is a necessary and informative tool in oncology clinical trials. *J Pathol.* 2014 Jan;232(2):185-9.

Clinical trials are essential for the improvement of cancer care. The complexity of modern cancer care and research require careful design, for which input from all disciplines is necessary. Pathologists should play a key role in the design and execution of modern cancer trials, with special attention to the eligibility, stratification and evaluation of response to therapy. In the current review all these aspects are discussed, with examples from colorectal cancer trials. We describe critical issues in biomarker evaluation and development and emphasize the importance of the role of the pathologist in quality control of cancer treatment.

Nishi A, Milner DA Jr, Giovannucci EL, Nishihara R, Tan AS, Kawachi I, Ogino S. Integration of molecular pathology, epidemiology and social science for global precision medicine. *Expert Rev Mol Diagn.* 2016;16(1):11-23.

The precision medicine concept and the unique disease principle imply that each patient has unique pathogenic processes resulting from heterogeneous cellular genetic and epigenetic alterations and interactions between cells (including immune cells) and exposures, including dietary, environmental, microbial and lifestyle factors. As a core method field in population health science and medicine, epidemiology is a growing scientific discipline that can analyze disease risk factors and develop statistical methodologies to maximize utilization of big data on populations and disease pathology. The evolving transdisciplinary field of molecular pathological epidemiology (MPE) can advance biomedical and health research by linking exposures to molecular pathologic signatures, enhancing causal inference and identifying potential biomarkers for clinical impact. The MPE approach can be applied to any diseases, although it has been most commonly used in neoplastic diseases (including breast, lung and colorectal cancers) because of availability of various molecular diagnostic tests. However, use of state-of-the-art genomic, epigenomic and other omic technologies and expensive drugs in modern healthcare systems increases racial, ethnic and socioeconomic disparities. To address this, we propose to integrate molecular pathology, epidemiology and social science. Social epidemiology integrates the latter two fields. The integrative social MPE model can embrace sociology, economics and precision medicine, address global health disparities and inequalities, and elucidate biological effects of social environments, behaviors and networks. We foresee advancements of molecular medicine, including molecular diagnostics, biomedical imaging and targeted

therapeutics, which should benefit individuals in a global population, by means of an interdisciplinary approach of integrative MPE and social health science.

Office of the Assistant Secretary for Planning and Evaluation; US Department of Health and Human Services. The Importance of Radiology and Pathology Communication in the Diagnosis and Staging of Cancer: Mammography as a Case Study. Washington, DC; 2010.

Today, cancer is one of the leading causes of death in the United States. The initial diagnosis of cancer is a complex process involving many healthcare specialists. Two physician specialties often at the center of this initial cancer diagnosis are radiology and pathology. *While neither radiologists nor pathologists are usually involved in direct patient care, their collective findings and interventions are responsible for subsequent cancer patient treatment and outcome.* The issue of workflows between radiology and pathology and the need for communication, correlation and resolution of discordant findings between the two groups to reduce diagnostic errors is the focus of this report. The report also discussed how tumor registries can benefit from these improved workflows.

Ogino S, et al. Integration of pharmacology, molecular pathology, and population data science to support precision gastrointestinal oncology. npj Precision Oncol. 2017; Vol. 1, Article number:40.

Precision medicine has a goal of customizing disease prevention and treatment strategies. Under the precision medicine paradigm, each patient has unique pathologic processes resulting from cellular genomic, epigenomic, proteomic, and metabolomic alterations, which are influenced by pharmacological, environmental, microbial, dietary, and lifestyle factors. Hence, to realize the promise of precision medicine, multi-level research methods that can comprehensively analyze many of these variables are needed. In order to address this gap, the integrative field of molecular pathology and population data science (i.e., molecular pathological epidemiology) has been developed to enable such multi-level analyses, especially in gastrointestinal cancer research. Further integration of pharmacology can improve our understanding of drug effects, and inform decision-making of drug use at both the individual and population levels. Such integrative research demonstrated potential benefits of aspirin in colorectal carcinoma with PIK3CA mutations, providing the basis for new clinical trials. Evidence also suggests that HPGD (15-PDGH) expression levels in normal colon and the germline rs6983267 polymorphism that relates to tumor CTNNB1 (β -catenin)/WNT signaling status may predict the efficacy of aspirin for cancer chemoprevention. As immune checkpoint blockade targeting the CD274 (PD-L1)/PDCD1 (PD-1) pathway for microsatellite instability-high (or mismatch repair-deficient) metastatic gastrointestinal or other tumors has become standard of care, potential modifying effects of dietary, lifestyle, microbial, and environmental factors on immunotherapy need to be studied to further optimize treatment strategies. *With its broad applicability, our integrative approach can provide insights into the interactive role of medications, exposures, and molecular pathology, and guide the development of precision medicine.*

Pillay B, Wootten AC, Crowe H, Corcoran N, Tran B, Bowden P, Crowe J, Costello AJ. The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: A systematic review of the literature. Cancer Treat Rev. 2016 Jan;42:56-72.

BACKGROUND: Conducting regular multidisciplinary team (MDT) meetings requires significant investment of time and finances. It is thus important to assess the empirical benefits of such practice. A systematic review was conducted to evaluate the literature regarding the impact of MDT meetings on patient assessment, management and outcomes in oncology settings.

METHODS: Relevant studies were identified by searching OVID MEDLINE, PsycINFO, and EMBASE databases from 1995 to April 2015, using the keywords: multidisciplinary team meeting* OR multidisciplinary discussion* OR multidisciplinary conference* OR case review meeting* OR multidisciplinary care forum* OR multidisciplinary tumour board* OR case conference* OR case discussion* AND oncology OR cancer. Studies were included if they assessed measurable outcomes, and used a comparison group and/or a pre- and post-test design.

RESULTS: Twenty-seven articles met inclusion criteria. There was limited evidence for improved survival outcomes of patients discussed at MDT meetings. Between 4% and 45% of patients discussed at MDT meetings experienced changes in diagnostic reports following the meeting. **Patients discussed at MDT meetings were more likely to receive more accurate and complete pre-operative staging, and neo-adjuvant/adjuvant treatment.** Quality of studies was affected by selection bias and the use of historical cohorts impacted study quality.

CONCLUSIONS: **MDT meetings impact upon patient assessment and management practices.** However, there was little evidence indicating that MDT meetings resulted in improvements in clinical outcomes. Future research should assess the impact of MDT meetings on patient satisfaction and quality of life, as well as, rates of cross-referral between disciplines.

Rodriguez-Canales J, Eberle FC, Jaffe ES, Emmert-Buck MR. Why is it crucial to reintegrate pathology into cancer research? Bioessays. 2011 Jul;33(7):490-8.

The integration of pathology with molecular biology is vital if we are to enhance the translational value of cancer research. Pathology represents a bridge between medicine and basic biology, it remains the gold standard for cancer diagnosis, and it plays an important role in discovery studies. In the past, pathology and cancer research were closely associated; however, the molecular biology revolution has shifted the focus of investigators toward the molecular alterations of tumors. The reductionist approach taken in molecular studies is producing great insight into the inner workings of neoplasia, but it can also minimize the importance of histopathology and of understanding the disease as a whole. In turn, pathologists can underestimate the role of molecular studies in developing new ancillary techniques for clinical diagnosis. **A multidisciplinary approach that integrates pathology and molecular biology within a translational research system is needed. This process will require overcoming cultural barriers and can be achieved through education, a more effective incorporation of pathology into biological research, and conversely an integration of biological research into the pathology laboratory.**

Salto-Tellez M, James JA, Hamilton PW. Molecular pathology - the value of an integrative approach. Mol Oncol. 2014 Oct;8(7):1163-8.

Molecular Pathology (MP) is at the heart of modern diagnostics and translational research, but the controversy on how MP is best developed has not abated. **The lack of a proper model or trained pathologists to support the diagnostic and research missions makes MP a rare commodity overall.** Here we analyse the scientific and technology areas, in research and diagnostics, which are encompassed by MP of solid tumours; we highlight the broad overlap of technologies and analytical capabilities in tissue research and diagnostics; and we describe an integrated model that rationalizes technical know-how and pathology talent for both. The model is based on a single, accredited laboratory providing a single standard of high-quality for biomarker discovery, biomarker validation and molecular diagnostics.

Scarberry K, Ponsky L, Cherullo E, Larchian W, Bodner D, Cooney M, Ellis R, MacLennan G, Johnson B, Tabayoyong W, Abouassaly R. Evaluating the impact of the genitourinary multidisciplinary tumour board: Should every cancer patient be discussed as standard of care? Can Urol Assoc J. 2018 May 14.

INTRODUCTION: We sought to prospectively evaluate the effectiveness of the multidisciplinary tumour board (MTB) on altering treatment plans for genitourinary (GU) cancer patients.

METHODS: All GU cancer patients seen at our tertiary care hospital are discussed at MTB. We prospectively collected data on adult patients discussed over a continuous, 20-month period. Physicians completed a survey prior to MTB to document their opinion on the likelihood of change in their patient's treatment plan. Logistic regression was used to assess for factors associated with a change by the MTB, including patient age or sex, malignancy type, the predicted treatment plan, and the provider's years of experience or fellowship training.

RESULTS: A total of 321 cancer patients were included. Patients were primarily male (84.4%) with a median age of 67 (range 20-92) years old. Prostate (38.9%), bladder (31.8%), and kidney cancer (19.6%) were the most common malignancies discussed. A change in management plan following MTB was observed in 57 (17.8%) patients. The physician predicted a likely change in six (10.5%) of these patients. Multivariate logistic regression did not determine physician prediction to be associated with treatment plan change, and the only significant variable identified was a plan to discuss multiple treatment options with a patient (odds ratio 2.46; 95% confidence interval 1.09-9.54).

CONCLUSIONS: Routine discussion of all urologic oncology cases at MTB led to a change in treatment plan in 17.8% of patients. Physicians cannot reliably predict which patients have their treatment plan altered. Selectively choosing patients to be presented likely undervalues the impact of a multidisciplinary approach to care.

Schmidt HM, Roberts JM, Bodnar AM, Kunz S, Kirtland SH, Koehler RP, Hubka M, Low DE. Thoracic multidisciplinary tumor board routinely impacts therapeutic plans in patients with lung and esophageal cancer: a prospective cohort study. Ann Thorac Surg. 2015 May;99(5):1719-24.

BACKGROUND: National and subspecialty guidelines for lung and esophageal cancers recommend treatment decisions to be made in a multidisciplinary tumor board (MTB). This study prospectively analyzes the actual impact of presentation at the thoracic tumor board on decision making in thoracic cancer cases.

METHODS: During the electronic submission process for presentation at MTB managing physicians documented their current treatment plan. The initial treatment plan was compared with the MTB final recommendation. Patient demographics, physician's proposed treatment plan, MTB recommendation, and documentation of application of MTB recommendations were prospectively recorded in an Institutional Review Board approved database.

RESULTS: Between June 2010 and December 2012, 185 patients with esophageal and 294 patients with lung cancer were presented at the MTB. One hundred sixty-six patients were presented on more than 1 occasion, resulting in 724 assessments of 479 patients. In 48 esophageal cancer patients (26%) and 118 lung cancer patients (40%) MTB recommendations differed from the initial treatment plan. Overall, a differing MTB recommendation from the primary treatment plan occurred in 330 of 724 case presentations (46%). The MTB recommendations changed treatment plans in 40% and staging and assessment plans in 60% of patients. Follow-up in a cohort of 249 patients confirmed that MTB recommendations were followed in 97% of cases.

CONCLUSIONS: This study validates the impact of the thoracic MTB. Recommendations will differ from the managing providers' initial plan in 26% to 40% of cases. However, MTB recommendations can be successfully initiated in the majority of patients. Complex thoracic cancer patients will benefit from multidisciplinary review and should ideally be presented at tumor board.

Sholl LM, Aisner DL, Allen TC, Beasley MB, Borczuk AC, Cagle PT, Capelozzi V, Dacic S, Hariri L, Kerr KM, Lantuejoul S, Mino-Kenudson M, Raparia K, Rekhtman N, Roy-Chowdhuri S, Thunnissen E, Tsao MS, Yatabe Y; Members of Pulmonary Pathology Society. Programmed Death Ligand-1 Immunohistochemistry--A New Challenge for Pathologists: A Perspective From Members of the Pulmonary Pathology Society. Arch Pathol Lab Med. 2016 Apr;140(4):341-4.

The binding of programmed death ligand-1 and ligand-2 (PD-L1 and PD-L2) to PD-1 blocks T-cell-mediated immune response to tumor. Antibodies that target programmed death receptor-1 (PD-1) will block the ligand-receptor interface, thereby allowing T cells to attack the tumor and increase antitumor immune response. In clinical trials, PD-1 inhibitors have been associated with an approximately 20% overall response rate in unselected patients with non-small cell lung cancer, with sustained tumor response in a subset of patients treated by these immune checkpoint inhibitors. Facing a proliferation of PD-L1 immunohistochemistry clones, staining platforms, and scoring criteria, the pathologist must decide on the feasibility of introducing a newly approved companion diagnostic assay that may require purchase not only of a specific antibody kit but of a particular staining platform. Given the likely reality that clinical practice may, in the near future, demand access to 4 different PD-L1 antibodies coupled with different immunohistochemistry platforms, laboratories will be challenged with deciding among this variety of testing methods, each with its own potential benefits. Another immediate challenge to PD-L1 testing in lung cancer patients is that of access to adequate tumor tissue, given that non-small cell lung cancer samples are often extremely limited in size. With PD-L1 testing it has become clear that the historically used US regulatory approach of one assay-one drug will not be sustainable. One evolving concept is that of complementary diagnostics, a novel regulatory pathway initiated by the US Food and Drug Administration, which is distinct from companion diagnostics in that it may present additional flexibility. Although pathologists need to face the practical reality that oncologists will be asking regularly for the PD-L1 immunohistochemistry status of their patients' tumors, we should also keep in mind that there may be room for improvement of biomarkers for immunotherapy response. The field is rich with opportunities for investigation into biomarkers of immunotherapy response, particularly in the form of collaborative, multidisciplinary studies that incorporate oncologists, pathologists, and basic scientists. Pathologists must take the lead in the rational incorporation of these biomarkers into clinical practice.

Sorace J, Aberle DR, Elimam D, Lawvere S, Tawfik O, Wallace WD. Integrating pathology and radiology disciplines: an emerging opportunity? BMC Med. 2012 Sep 5;10:100.

Pathology and radiology form the core of cancer diagnosis, yet the workflows of both specialties remain ad hoc and occur in separate "silos," with no direct linkage between their case accessioning and/or reporting systems, even when both departments belong to the same host institution. Because both radiologists' and pathologists' data are essential to making correct diagnoses and appropriate patient management and treatment decisions, this isolation of radiology and pathology workflows can be detrimental to the quality and outcomes of patient care. These detrimental effects underscore the need for pathology and radiology workflow integration and for systems that facilitate the synthesis of all data produced by both specialties. With the enormous technological

advances currently occurring in both fields, the opportunity has emerged to develop an integrated diagnostic reporting system that supports both specialties and, therefore, improves the overall quality of patient care.

Tan MP, Ong EM, Amy D, Tot T. Integrating anatomy, radiology, pathology, and surgery: An alternative approach in resecting multifocal and multicentric breast carcinoma. *Breast J.* 2017 Nov;23(6):663-669.

The sick lobe hypothesis provides the basis for a lobar approach in radiology, pathology, and surgical treatment of breast cancer. This approach aims to remove the tumor together with the surrounding field of genetic aberrations. Detailed preoperative lobar imaging that properly maps the disease and assesses its extent guides the parenchymal resection. Integration of our knowledge of breast anatomy and pathology with the results of preoperative radiological mapping is critical in assessing the eligibility of patients with multifocal and/or multicentric breast cancer for breast conservation treatment. Through an appropriately selected incision, a multisegment resection of the diseased lobe(s) is performed, which leaves the residual parenchyma in a formation that allows dovetailing of one part into the other, like the way pieces of a jigsaw puzzle fit together. **Detailed pathologic analysis of the surgical specimen provides valuable feedback to the radiologist, establishes the completeness of surgical intervention, and generates predictive information for therapeutic decisions.** Our approach is a step in continuous search for ideal tailored therapy to avoid under or over-treatment of breast cancer patients.

References

¹ 2018 ACCC Survey. *Understanding the Landscape of Pathology Integration with the Cancer Care Team.* Question 10.

² 2018 ACCC Survey. *Understanding the Landscape of Pathology Integration with the Cancer Care Team.* Question 13.

³ 2018 ACCC Survey. *Understanding the Landscape of Pathology Integration with the Cancer Care Team.* Question 18.

⁴ CMS finalizes coverage of Next Generation Sequencing tests, ensuring enhanced access for cancer patients
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